Initiation of Systemic Therapy During the Last 30 Days of Life in Patients With Metastatic Castration-Resistant Prostate Cancer

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Abstract. Background/Aim: Compared to intravenous taxane chemotherapy, newer orally available and/or less toxic agents for metastatic castration-resistant prostate cancer (MCRPC) may be associated with higher likelihood of starting treatment in patients with adverse prognostic features and limited life expectancy. To test this hypothesis, we analyzed the rates of treatment initiation during the last 30 days of life in a real-world cohort of men with MCRPC. Patients and Methods: This was a retrospective analysis of 146 patients. Results: Seven patients (5%) who started any systemic treatment during the last 30 days of life were identified. The likelihood of treatment initiation in the last 30 days of life correlated significantly with the number of lines of systemic treatment (higher risk for >= second line) and non-use of bone-targeted agents. Conclusion: Initiation of systemic therapy in the last 30 days of life was uncommon. This endpoint might complement other quality-of-care indicators.

Over the last decade, systemic treatment for metastatic castration-resistant prostate cancer (MCRPC) has improved (1, 2). New options such as abiraterone acetate, enzalutamide and Ra-223 have been approved (3-10). In contrast to docetaxel and cabazitaxel (11-13), two of these new therapies do not require intravenous administration. All three were shown to cause fewer side effects than taxanes (3, 5, 8, 14). Reluctance to prescribe taxanes may be greater in patients with poor performance status, older age and certain comorbidities. Due to their side effect profile and, in part, oral route of administration, clinicians may be less restrictive in prescribing abiraterone acetate, enzalutamide or Ra-223 in patients with adverse prognostic features, many of whom are expected to have very limited life expectancy. Therefore, we hypothesized that the availability of these newer drugs may increase the likelihood of initiating a new line of treatment close to the end of life, *i.e.* the last 30 days of life. Numerous studies have shown that rates of administration of chemotherapy during the last 30 days of life (a quality-of-care indicator) remain too high (15-18). Overutilization of radiotherapy also contributes to sub-optimal use of health care resources (19-22). Due to difficulties in estimating the remaining lifespan, termination of systemic treatment in due time may sometimes be challenging. In contrast, initiation of a new treatment is often more complex and thus potentially easier to prevent than continuation of an already ongoing treatment. Therefore, the rate of initiation of a new treatment in the last 30 days of life was evaluated in a patient population treated in a well-defined geographical region with a publicly-funded healthcare system that provides equal access to treatment irrespective of income, place of living and other potential socioeconomic barriers.

Patients and Methods

Patients and treatment

A retrospective single-institution study that included all consecutive patients with MCRPC who received systemic treatment at Nordland Hospital in Bodø, Norway was performed. The primary endpoint was initiation of a new treatment in the last 30 days of life, and therefore only patients who had died before data extraction in June 2017 were included. Overall, the study population consisted of 146 men. They were identified from the electronic patient record (EPR) systems of the hospital and had received at least one dose of systemic therapy (abiraterone acetate, enzalutamide, taxotere, cabazitaxel, Ra-223, denosumab or zoledronic acid). Formal assessment of a patient's prognosis, *e.g*., by nomogram or score was not required when starting new treatments.

Statistical methods

All analyses were performed with SPSS 23 (IBM, New York, NY, USA). Actuarial survival from imaging diagnosis of distant metastases was calculated with the Kaplan–Meier method. Date of death was known in all patients. Associations between different variables of interest were assessed with the chi-square or Fisher exact probability test (two-tailed). A *p*-value ≤0.05 was considered statistically significant.

Results

Patient characteristics

The median age (range) at diagnosis of prostate cancer, distant metastases, and death was 68 years (range=51-89 years), 72.5 (range=56-89 years), and 76 (range=57-96 years), respectively. Forty-nine patients (34%) had distant metastases at the time of

diagnosis of prostate cancer. The majority (n=97, 66%) had metachronous metastatic disease after a median of 67 months from initial cancer diagnosis (range 3-244). In the latter group, 62 patients had developed MCRPC when they were diagnosed with distant metastases. When diagnosed with metastatic disease, 107 patients (73%) had bone-only involvement and 35 (24%) bone and lymph node metastases, most commonly in the abdomen and/or thorax. Only 4 patients (3%) had visceral distant metastases. Further information is shown in Table I.

Systemic treatment

During the time period of this study our institution followed the pathways outlined in the national Norwegian guidelines for management of prostate cancer. The public health care system is based on strong adherence to these guidelines, providing equal access to high-quality care irrespective of place of living (9). Regular updates ensured that new drugs became available after their approval by the European Medical Agency. None of our patients participated in a clinical trial or early access program. All of them received standard treatment, which however evolved every time new therapies were introduced. Early during the study period, treatment consisted of endocrine therapy including total androgen blockade followed by anti-androgen withdrawal, and after development of MCRPC prednisolone and taxotere, maybe followed by mitoxantrone. Stepwise, further options (cabazitaxel, abiraterone acetate, and enzalutamide) became available. All patients continued on luteinizing hormone–releasing hormone (LHRH) agonists, unless bilateral orchiectomy had been performed. Individualized decisions were made regarding the sequence of treatments. Forty-seven patients (32%) were treated during the time period when abiraterone acetate was approved by the Norwegian regional health authorities, the first modern non-taxane treatment

option. The other patients were treated in the earlier docetaxel era. Overall, 10 patients (7%) received Ra-223 and 5 (3%) strontium-based radionuclide therapy. External bone irradiation was common (n=120, 82%). Further information is shown in Table II.

Survival and primary endpoint

Median overall survival with metastatic disease was 26.6 months (68.5 months from first cancer diagnosis). When calculated from diagnosis of distant metastases, survival was less than 6 months in 9 patients (6%) and 6-12 months in 15 patients (10%).

Overall, 7 patients (5%) started a new treatment during the last 30 days of life. The rates were not significantly different in the two time periods, *i.e*. the taxane-only era and the abiraterone acetate/enzalutamide/Ra-223 era (6 *vs*. 4%, *p*=0.68). Two of the 7 patients, both older than 70 years, died from chemotherapy toxicity. The treatment sequence was taxotere, abiraterone acetate, enzalutamide and cabazitaxel in one of these patients. The other patient had received taxotere as first-line approach. Information about all 7 patients is shown in Table III. In 5 of them, death was considered unrelated to toxicity, meaning that the estimation of the patients' prognosis was overly optimistic.

Overall, 9% of the patients were irradiated within the last 30 days of life (radionuclide in 1 case, external beam in 12 cases). The most common scenario was external beam radiotherapy for bone pain (n=9). The rate of radiotherapy in the last 30 days of life correlated with the rate of initiation of systemic treatment in the same time period (*p*=0.02). Out of 7 patients with systemic treatment initiation, 3 (43%) also had radiotherapy. Out of 139 patients without initiation of systemic therapy in the last 30 days, only 7% (n=10) had radiotherapy. Table IV shows other statistically significant correlations between treatment initiation and patient- or treatment-related factors.

Discussion

During the last 15 years, several new systemic treatment options for patients with MCRPC have become available. The first one was docetaxel (11). Approximately the same magnitude of survival improvement was seen with cabazitaxel (12), abiraterone acetate (3), enzalutamide (5), and Ra-223 (8). None of these treatments is able to prevent death from MCRPC (23-25). In a previous study of aggressive end-of-life care that included approximately 1500 patients with metastatic prostate cancer younger than age 65 years, slightly more than 10% received chemotherapy within the last 14 days of life (17). This quality-of-care indicator, together with other endpoints, has repeatedly been reported in a broad range of oncology studies (26-28). Reducing overly aggressive end-of-life care is warranted from a patient, caregiver/family and payer/health-care administrator perspective. In the present study, we focused on a different endpoint that may be assessed in a comprehensive quality-of-care analysis, namely initiation of systemic treatment in the last 30 days of life. We became interested in this endpoint because we were worried about the possibility that orally available and/or rather well-tolerated agents, such as abiraterone acetate, enzalutamide and Ra-223, would reduce physicians' reluctance to initiate treatment in poor-prognosis patients, compared to taxane-based chemotherapy. Traditionally, a critical assessment of age, frailty, comorbidity, performance status and organ function has resulted in restricted chemotherapy use in patients with unfavorable risk-benefit-ratio in our clinical practice. The choice of endpoint was also influenced by the uncertainty of retrospective assessment of oral medications in ambulatory patients with terminal prostate cancer, which may result in under-reporting.

It was reassuring to see that only 5% of the patients started a new systemic treatment during the last 30 days of life, even when applying a broad definition of systemic treatment, which included bone-targeted agents. The drugs that were hypothesized to lower the barrier for treatment initiation were not overrepresented. However, due to the small number of events, our study had limited statistical power and this fact may also have hampered our ability to identify patient-related risk factors such as performance status (PS). A strict policy of limiting treatment initiation to patients with PS 0-2 would have reduced our rate from 5 to 3%. The fact that the primary endpoint also was associated with palliative radiotherapy in the last 30 days of life and that very short PSA-doubling time was common, suggests that symptom burden might have influenced the decision to start systemic therapy. Even in appropriately selected patients, active systemic therapy might cause serious and sometimes fatal toxicities. Also, in our study, two patients died from taxane-related side effects. The risk of starting treatment in the last 30 days of life was lowest in patients who started with bone-targeted agents (2%), followed by first-line chemotherapy/abiraterone acetate/enzalutamide/Ra-223 (4%). For second- and third- line treatment with one of these agents, risk increased to 7-8%. This finding probably reflects the disease biology and timeline of progression.

Patients managed without bone-targeted agents were at higher risk (16%) of starting a new treatment, compared to those who received such agents, either alone or in combination with other drugs. Possibly, there was a large burden of visceral metastases in cases where bone-targeted agents were omitted, which would result in shorter survival (29). However, our database did not contain information about patterns of spread for each time-point of treatment initiation.

Bergman *et al.* reported that chemotherapy was never initiated within 3 months of death, however in a small study of 60 men, all of whom uninsured, with low income and enrolled in a public assistance program (30). Besides patient selection, this study was performed in the docetaxel-only era. In a prospective randomized trial of docetaxel/estramustine *vs.* mitoxantrone less than 3% of the patients died within 30 days of enrollment (31). In a different study, less than 3% of the patients died from cabazitaxel-related toxicity (32). In a study that was not limited to men with prostate cancer, 4% of the patients died within 30 days of the first cycle of a new course of chemotherapy (33). The study included 1131 patients, but did not collect data on endocrine treatment. Compared to these heterogeneous studies, our rate of 5% (including even bone-targeted agents) is not alarmingly high. We recommend large-scale studies with higher statistical power to firmly reject the hypothesis that treatment initiation in the last 30 days of life is more common for orally available and/or less toxic agents such as abiraterone acetate, enzalutamide and Ra-223.

Conclusion

Initiation of systemic therapy in the last 30 days of life was uncommon and not clearly related to any particular class of agents. In contrast, its likelihood was higher in patients who had received systemic treatment before. This endpoint might complement other quality-of-care indicators such as rate of administration of systemic therapy in the last 2 weeks of life.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

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Table I. Patient characteristics at the time of diagnosis with prostate cancer (n=146).

Parameter	n	%
Married/partner	111	76
Single	29	20
Unknown	6	4
Place of living: Bodø[a]	66	45
Place of living: surrounding communities	80	55
Charlson comorbidity index 0	75	51
Charlson comorbidity index 1	44	30
Charlson comorbidity index >1	17	12
Unknown	10	7
Gleason score ≥8	82	56
Gleason score <8	64	44
NCCN risk category at first cancer diagnosis: M1	49	34
NCCN risk category at first cancer diagnosis: N1	12	8
NCCN risk category at first cancer diagnosis: high/very high	56	38
NCCN risk category at first cancer diagnosis: intermediate	29	20
Initial surgical treatment	15	10
Initial radiotherapy ± endocrine treatment	14	10
Initial LHRH agonist	72	49
Initial antiandrogen	14	10
Initial orchiectomy	5	3
Initial watchful waiting	26	18
Less than 5 bone metastases (isotope bone scan)[b]	43	30
At least 5 bone metastases[b]	91	62
Unknown[b]	12	8

[a]approximately 50,000 inhabitants; surrounding communities: approximately 80,000 inhabitants;
[b]at the time of diagnosis of metastatic disease.
NCCN: National Comprehensive Cancer Network; LHRH: luteinizing hormone–releasing hormone.

Table II. Systemic therapy after diagnosis of distant metastases (n=146).

Parameter	n	%
Overall systemic therapy: bone-targeting only	46	32
Overall systemic therapy: chemo only[a]	25	17
Overall systemic therapy: both	75	51
One line only[a]	93	64
Two or more lines[a]	53	36
Received any taxotere	86	59
Received any mitoxantrone	8	6
Received any cabazitaxel	6	4
Received abiraterone acetate after chemotherapy	37	25
Received abiraterone acetate before chemotherapy	12	8
Received enzalutamide after chemotherapy	17	12
Received Ra-223	10	7

[a] includes cytotoxic chemotherapy, abiraterone acetate, enzalutamide, Ra-223.

Table III. Patients who started systemic treatment in the last 30 days of life (n=7, including two patients who died from toxicity within 30 days of chemotherapy administration).

Patient nr.	Index treatment	Previous treatment	Age, years	ECOG PS	PSA doubling time, months
1	Abiraterone acetate	Enzalutamide	75	3	<2
2	Abiraterone acetate	Taxotere	60	1	<2
3	Zoledronic acid	None	72	3	<2
4	Enzalutamide	A followed by T*	76	1	2.5
5	Enzalutamide	None	80	2	<2
6	Cabazitaxel	T - A - E**	73	1	4
7	Taxotere	None	74	2	<2

ECOG PS: Eastern Cooperative Oncology Group performance status; PSA; prostate-specific antigen.
* Abiraterone acetate followed by taxotere;
** Taxotere followed by abiraterone acetate and then enzalutamide.

Table IV. Associations between initiation of systemic treatment in the last 30 days of life (IST30) and different patient- or treatment-related parameters.

Primary endpoint	Parameter	Patient numbers	*p*-Value (Fisher exact probability test)	Likelihood of IST30
IST30	RT30 yes/no	3, 4	0.02	
No IST30	RT30 yes/no	10, 129		
IST30	BT yes/no	3, 4	0.02	No bisphosphonate or denosumab: 16%
No IST30	BT yes/no	21, 118		Bisphosphonate or denosumab: 2%
IST30	Overall Tx 1/2/3	1, 4, 2	0.02	Group 2: 16%
No IST30	Overall Tx 1/2/3	45, 21, 73		Group 1: 2%, group 3: 3%
IST30	Lines B/1/2/3	1, 2, 2, 2	0.001 (Chi square test)	Group 3: 8%, group 2: 7%
No IST30	Lines B/1/2/3	43, 47, 27, 22		Group B: 2%, group 1: 4%

RT30: Received radiotherapy in the last 30 days of life; BT: received any bisphosphonate or denosumab, overall Tx (treatment) 1: bone-targeted only; 2: chemotherapy/abiraterone acetate/enzalutamide without bone-targeted agents; 3: chemotherapy/abiraterone acetate/enzalutamide with bone-targeted agents; Lines B: bone-targeted only; 1: 1 line of chemotherapy/abiraterone acetate/enzalutamide/Ra-223; 2: 2 lines, 3: 3 or more lines.
All other parameters including age, comorbidity, synchronous vs. metachronous metastases, and place of living were not significant.